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AURKC mutation beyond macrozoospermia: a case report and literature review on a novel exon 7 variant linked to acephalic sperm morphology

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Abstract

Acephalic spermatozoa syndrome is a rare and severe form of teratozoospermia caused by defects in the head–tail coupling apparatus. Several genes, including SUN5, PMFBP1, and TSGA10, have been implicated. AURKC mutations, however, are traditionally associated with macrozoospermia and have not previously been linked to this syndrome. We report a consanguineous case of male infertility characterized by >90% acephalic spermatozoa and a novel heterozygous missense mutation in exon 7 of the AURKC gene (c.203A>G, p.Arg→Gly). This mutation has not been previously described in association with any sperm morphology defect other than macrozoospermia. The patient had no history of macrocephalic sperm, and standard semen analysis confirmed a monomorphic acephalic phenotype. This is the first report of a heterozygous AURKC exon 7 mutation associated with acephalic spermatozoa syndrome. The case expands the known phenotypic spectrum of AURKC-related infertility and highlights the importance of full-gene sequencing in patients with severe sperm morphological abnormalities.

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Introduction

Infertility is recognized by the World Health Organization as a disease of the reproductive system and affects approximately 17.5% of the adult population worldwide, with regional estimates ranging from 11% to 23% (1). Male factors are involved in up to 50% of these cases. Evaluation of male infertility typically begins with semen analysis. While mild abnormalities may have multifactorial origins, severe forms of teratozoospermia, including rare conditions like acephalic spermatozoa syndrome, are often genetically determined (2).

Acephalic spermatozoa syndrome is characterized by spermatozoa lacking heads due to failure of the head–tail coupling apparatus (HTCA) during spermiogenesis. This morphological anomaly leads to a total inability of the sperm to fertilize the oocyte naturally or via intracytoplasmic sperm injection (ICSI) (3,4). The condition is further categorized into three subtypes based on the precise structural disconnection within the coupling apparatus.

Genetic studies have identified mutations in several genes; including SUN5, PMFBP1, HOOK1, and TSGA10 as contributing to this morphological defect (5,6). Notably, only mutations in SUN5 and PMFBP1 are well-established as being implicated in acephalic spermatozoa syndrome (3). In contrast, AURKC, encoding Aurora kinase C, a member of the Aurora kinase family critical for chromosomal segregation, is primarily associated with macrozoospermia due to meiotic failure (7). Beyond male infertility, aberrant AURKC activity has been linked to chromosomal instability in cancers (8,9), though its role in head–tail coupling defects remains unreported. Our case is the first to propose a potential association between a mutation in AURKC and acephalic spermatozoa syndrome, thereby suggesting

Key point

A consanguineous male patient presented with severe teratozoospermia marked by more than 90 percent acephalic spermatozoa. Genetic testing identified a previously unreported heterozygous missense mutation in exon 7 of the AURKC gene (c.203A>G, p.Arg>Gly), a gene typically linked to macrozoospermia rather than head–tail detachment defects. The patient showed no macrocephalic sperm and exhibited a uniform acephalic morphology on semen analysis. This case represents the first association between an exon 7 AURKC variant and acephalic spermatozoa syndrome, extending the known phenotypic spectrum of AURKC-related male infertility and underscoring the value of comprehensive gene sequencing in patients with severe sperm morphological abnormalities.

a broader role for this gene in the etiology of sperm structural defects. This report describes a patient with over 90% headless sperm phenotype and a novel mutation in exon 7 of AURKC, and reviews the gene's potential involvement in severe teratozoospermia.

Case Presentation

A 31-year-old male presented with a 5-year history of primary infertility. He made an appointment at the reproductive medicine unit of the Royan institute. He had no history of testicular trauma, infections, varicocele, or exposure to gonadotoxic agents. His partner's gynecologic evaluation was unremarkable. His hormonal profile, including FSH, LH, testosterone, and prolactin was within normal ranges. While his parents were consanguineous, the relationship was distant, and there was no known history of infertility among his relatives.

The patient had previously participated in a genetic study involving individuals diagnosed with acephalic spermatozoa syndrome, during which he underwent a comprehensive genetic workup including targeted analysis of the AURKC gene.

Semen analysis

Two sperm analyses were performed; one in July 2020 and the latest in March 2023. The results confirmed persistent acephalic sperm morphology in more than 90% of spermatozoa (Figure 1). Table 1 summarizes the key findings from both tests.

Genetic and PCR analysis

To investigate the genetic basis for the headless sperm phenotype, genomic DNA was extracted from peripheral blood using the salting-out method. DNA purity was confirmed by NanoDrop spectrophotometry (260/280 ≈ 1.8).

Primer design and PCR conditions

Primers were designed to target exon 7 of AURKC:

- Forward primer: 5′-CCTTTGGGCATTCATGGG-3′
- Reverse primer: 5′-ACCCAGTCACATAATAACTCAC-3′

PCR was carried out in 25 µL volumes using 2.5 µL 10× buffer, 1.5 mM $MgCl_2$, 0.2 mM dNTPs, 0.5 µM primers, 1 U Taq polymerase, and 50–100 ng genomic DNA.

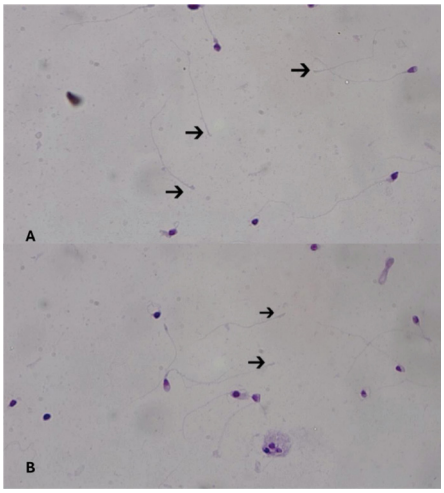

Figure 1. A and B; High-power field image (×400 magnification) of a semen smear from the patient showing morphologically abnormal spermatozoa (acephalic type) highlighted with arrows.

Thermocycling conditions

Initial denaturation at 95 °C for 3 minutes followed by 31 cycles of 95 °C for 30 s, 58 °C for 30 s, and 72 °C for 30 s with a final extension at 72 °C for 5 minutes.

Electrophoresis of PCR products showed a 515 bp band, confirming successful amplification. Products were sequenced and analyzed using Finch TV and aligned to the AURKC reference sequence (NM_001012732.2).

A heterozygous single nucleotide variant, NM_001012732.2:c.203A>G, was identified in exon 7. This missense mutation results in an amino acid substitution at position 68 of the protein (NP_001012754.1:p.(Arg68Gly)), changing the codon from AGG (arginine) to GGG (glycine) (Figure 2).

Table 1. Semen analysis results from two independent tests performed in July 2020 and March 2023

Parameter	Test 1 (July 2020)	Test 2 (March 2023)
Sperm concentration (×10⁶/mL)	35	25
Progressive motility (%)	11%	8%
Non-progressive motility (%)	33%	37%
Total motility (%)	44%	Not specified
Normal morphology (%)	0%	0%
Pinhead sperm (per 200 cells)	110	120
Giant head count	1	2
Short tail count	15	18
Excess residual cytoplasm	10	2
WBC (×10⁶/mL, peroxidase positive)	0.6	0.5

Parameters are reported according to WHO criteria. The results demonstrate persistently abnormal sperm morphology with a high proportion of acephalic (pinhead) spermatozoa.

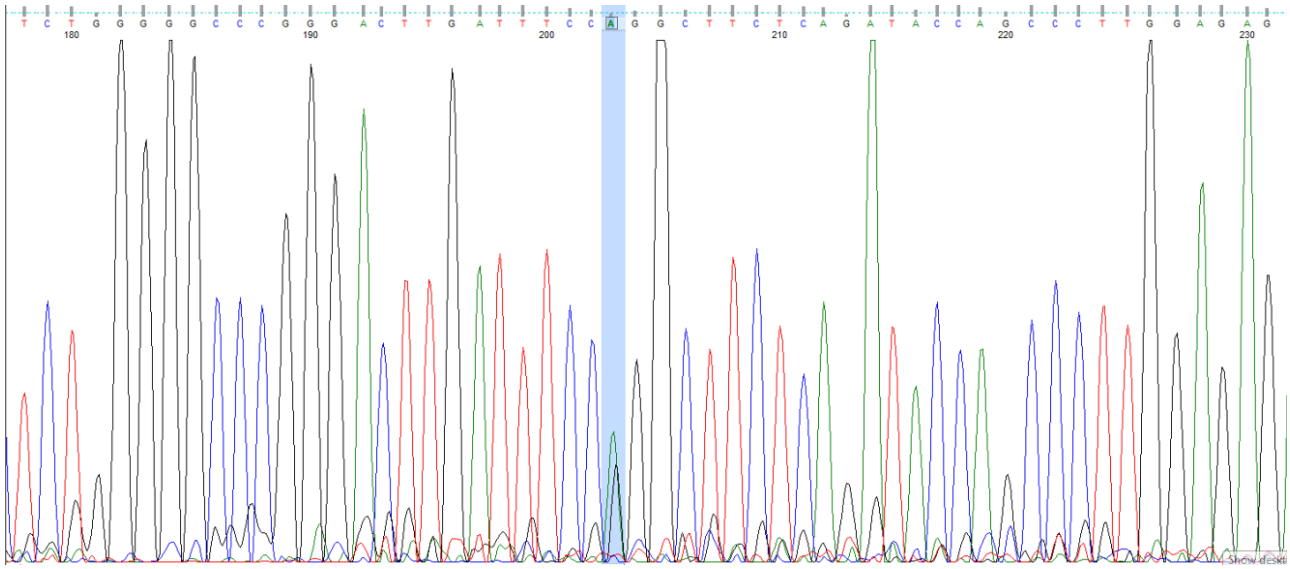

Figure 2. Partial sequencing chromatogram of exon 7 of the AURKC gene, analyzed using FinchTV software. The blue-highlighted region indicates the mutation site, showing a heterozygous A>G substitution at position 203. This single nucleotide variant results in an amino acid change from arginine (Arg) to glycine (Gly), detected in the patient diagnosed with acephalic spermatozoa syndrome.

In silico analysis

To assess the pathogenic potential of the *AURKC* c.203A>G (p.Arg68Gly) variant, a panel of in silico prediction tools was used. These included SIFT, PolyPhen-2, MutationTaster, CADD, REVEL, and BayesDel. Each algorithm evaluates the likely impact of amino acid substitutions on protein structure and function based on evolutionary conservation, sequence homology, and physicochemical properties. Additionally, population frequency data were obtained from the gnomAD v2.1.1 database.

All prediction tools consistently classified the variant as damaging or disease-causing, with scores surpassing established pathogenicity thresholds. Importantly, the variant was not present in gnomAD, supporting its rarity and potential clinical significance (Table 2).

Discussion

Acephalic spermatozoa syndrome is a rare and severe form of teratozoospermia, defined by the predominance of spermatozoa lacking heads in the ejaculate. This condition disrupts male fertility by preventing effective fertilization, as the head of the sperm carries the genetic material and fusion apparatus required for oocyte penetration (10). Morphologically, head–tail separation often occurs between the proximal centriole and the nuclear envelope during spermiogenesis, and in some cases, the detached tails may retain progressive motility (11). Based on electron microscopy and genetic analysis, the disorder is thought to stem from failure in the development or function of the HTCA, particularly at the implantation fossa and basal plate (12). This syndrome has been classified into three morphological subtypes based on the site of disjunction, which may correlate with underlying genetic causes and reproductive potential.

Genetic studies have identified several causative genes in patients with this syndrome, most notably SUN5, PMFBP1, and TSGA10, which encode proteins critical for anchoring the flagellum to the nucleus (13,14). SUN5 is currently the most commonly mutated gene in acephalic spermatozoa syndrome and is expressed at the head–tail junction during spermiogenesis (4). Other genes implicated include DNAH6, CEP112, HOOK1, and BRDT, though many of these remain of uncertain pathogenicity due to limited evidence (3). Table 3 provides a comparative summary of reported mutations and outcomes in acephalic

Table 2. In silico pathogenicity predictions for the c.203A>G (p.Arg68Gly) variant in exon 7 of the AURKC gene. The variant was analyzed using multiple computational tools

Tool	Prediction	Score/Threshold
SIFT	Damaging	0.02 (cutoff < 0.05)
PolyPhen-2	Probably damaging	0.998 (cutoff > 0.85)
MutationTaster	Disease-causing	1.0 (scale: 0–1)
CADD	Pathogenic	28.5 (cutoff > 20)
REVEL	Deleterious	0.85 (cutoff > 0.7)
BayesDel	Deleterious	0.40 (cutoff ≈ −0.05)
gnomAD frequency	Not reported (novel)	0 (not found in population databases)

All predictors indicated a high likelihood of pathogenicity. Additionally, the variant was not reported in the gnomAD database, supporting its novelty.

Table 3. Summary of reported gene mutations underlying acephalic spermatozoa syndrome (ASS) and macrozoospermia

Author (Ref.)	Gene (mutation(s))	Phenotype	Inheritance	Reproductive outcome	Notes/Highlights
Zhu et al (4)	SUN5 (biallelic, e.g. c.824C>T, p.Thr275Met)	Acephalic spermatozoa	Homozygous/ Compound AR	– (male infertility)	First report linking recessive SUN5 mutations to acephalic spermatozoa (head–tail detachment). Found *SUN5* variants in ~47% of ASS cases.
Elkhatib et al (25)	SUN5 (homozygous exon 8 deletion, p.Leu143Serfs*30)	Decapitated/ acephalic	Homozygous	–	Confirmed SUN5 loss-of-function causes ASS. Three unrelated men had identical deletion (frameshift), strengthening SUN5's role.
Zhang et al (12)	SUN5 (homozygous c.381delA, p.Val128Serfs*7)	Acephalic spermatozoa	Homozygous (AR)	–	Identified SUN5 frameshift variant in ASS patients; detailed molecular mechanism linking SUN5 loss to HTCA failure.
Fang et al (26)	SUN5 variants	Acephalic spermatozoa	AR (biallelic)	Favorable pregnancy via ICSI	Study of ASS couples with *SUN5* mutations showed that ICSI could achieve pregnancy; all couples (3/3) had successful fertilization and pregnancy, indicating *SUN5*-ASS is treatable by ICSI.
Zhu et al (14)	PMFBP1 (homozygous nonsense; compound het frameshift)	Acephalic spermatozoa	Homozygous/ Compound AR	Successful ICSI (human+mouse)	Discovered *PMFBP1* nonsense mutations in 3 ASS patients. Mouse knockout recapitulated headless sperm. Remarkably, ICSI overcame infertility in both mice and humans with these mutations.
Sha et al (27)	PMFBP1 (biallelic truncating)	Acephalic spermatozoa	Homozygous/ Compound AR	–	Clin Genet report confirming *PMFBP1* truncating mutations in two unrelated ASS patients. Localized *PMFBP1* at the head–tail junction; knockout mice phenocopied ASS.
Lu et al (28)	PMFBP1 (homozygous missense)	Acephalic spermatozoa	Homozygous	–	Case report identifying a novel *PMFBP1* missense variant in an ASS patient (homozygous). Supports *PMFBP1* as an ASS gene.
Sha et al (29)	TSGA10 (homozygous frameshift)	Acephalic spermatozoa	Homozygous	–	First implicating *TSGA10* in ASS. Found a homozygous frameshift variant; testis-specific *TSGA10* protein is disrupted in patient sperm.
Ye et al (13)	TSGA10 (homozygous frameshift c.545dupT, p.Ala183Serfs*10)	Acephalic spermatozoa	Homozygous	–	Case report of an ASS patient with a novel *TSGA10* frameshift. TEM showed misassembled mitochondrial sheath, but *SUN5* and *PMFBP1* were normal.
Khan et al (30)	TSGA10 (homozygous missense c.1112T>C, p.Leu371Pro)	Acephalic spermatozoa	Homozygous	–	Pakistani family WES found *TSGA10* missense variant cosegregating with ASS. Sperm ultrastructure (TEM) showed head–tail defects in patients.
Liu et al (31)	PMFBP1, TSGA10 (novel variants)	Acephalic spermatozoa	AR (biallelic)	High fertilization & pregnancy via ICSI	Small cohort (Clin Genet 2021) of 12 ASS men: 7 had mutations in *TSGA10* or *PMFBP1*. All such patients achieved fertilization/pregnancy by ICSI (100% fertilization rate).
Hua et al (18)	AURKC (homozygous missense c.269G>A)	Macrozoospermia	Homozygous	ICSI attempted – no embryos (failure)	Consanguineous family: WES found novel homozygous *AURKC* variant. qPCR showed reduced *AURKC* mRNA. ICSI yielded no usable embryos, underscoring the importance of AURKC for zygote formation.
Jiang et al (24)	AURKC (compound het c.434C>T + c.497A>T)	Macrozoospermia	Compound het AR	Successful ICSI → healthy live birth	First reported live birth from macrozoospermia with known *AURKC* variants. Husband's sperm had 100% large heads; couple selected appropriately sized sperm for ICSI, resulting in term birth of a healthy male.
Bai et al (20)	AURKC (compound het, novel mutations)	Macrozoospermia	Compound het AR	–	Report of an infertile man with macrozoospermia carrying two new heterozygous *AURKC* mutations. Illustrates genetic heterogeneity and confirms *AURKC* as the macrozoospermia gene.
Kobesiy et al (32)	AURKC variants in Egyptian patients	Macrozoospermia	AR (various)	–	Screening study found known *AURKC* founder deletion (c.144delC) in Egyptian macrozoospermia patients; reinforces that *AURKC* mutations (often truncating) are the predominant cause of human macrozoospermia.

Note: This table compares key literature reports of pathogenic mutations (genes and variants), clinical phenotypes, inheritance patterns, and reproductive outcomes in ASS or macrozoospermia, including the present AURKC exon 7 mutation case.

spermatozoa syndrome and macrozoospermia, including this case's AURKC mutation.

In the present case, we identified a novel heterozygous A>G mutation in exon 7 of the AURKC gene, leading to a p.Arg→Gly substitution. This variant has not been previously reported in the context of acephalic spermatozoa or any other sperm phenotype. The AURKC gene, located on chromosome 19q13.43, encodes Aurora kinase C, a serine/threonine kinase essential for chromosomal segregation during meiosis. It is strongly expressed in

spermatocytes and plays a key role in cytokinesis and germ cell ploidy control (2).

To date, AURKC mutations have been exclusively linked to macrozoospermia, a distinct and severe form of teratozoospermia in which all spermatozoa exhibit enlarged, round, often multinucleated heads, frequently accompanied by multiple flagella. More than 90% of such cases are caused by the recurrent c.144delC frameshift mutation in exon 3, though other pathogenic alleles have been identified in exons 5 and 6 (e.g., c.436-2A>G, c.744C>G) (15-18). Notably, no pathogenic variant has ever been reported in exon 7, making this the first case in which a mutation in this exon has been associated with a sperm defect.

AURKC-related macrozoospermia is inherited in an autosomal recessive manner. Affected men consistently carry homozygous or compound heterozygous mutations, while heterozygous carriers are phenotypically normal and fertile (19,20). For example, Dieterich et al and Ben Khelifa et al both demonstrated that heterozygous men showed no signs of macrozoospermia, while homozygotes presented with 100% large-headed sperm (7,16). Our patient, who carries a novel heterozygous mutation in exon 7, exhibited a pure acephalic sperm phenotype, with no signs of macrocephaly or other features of classical AURKC-related disease. Whether this represents a novel pathogenic mechanism or a modifying variant in a polygenic context remains to be investigated. Comprehensive sequencing and functional studies will be required to clarify the exact role of this variant in the pathogenesis of acephalic spermatozoa.

While assisted reproduction outcomes in such patients remain uncertain, several studies have reported successful ICSI in men with acephalic spermatozoa syndrome, particularly in cases involving SUN5, PMFBP1, and HOOK1 mutations. These patients, classified as subtype II, often achieve high fertilization and live birth rates when carefully selected head–tail-attached spermatozoa are used (21-23). In macrozoospermia, ICSI is generally discouraged due to meiotic failure and aneuploidy risk; however, a recent case reported a successful singleton live birth in a patient with 100% macrocephalic sperm and compound heterozygous AURKC mutations, achieved after careful selection of morphologically normal-appearing sperm (24).

Taken together, these findings emphasize the need for individualized reproductive planning in patients with severe sperm defects. Our report adds to the limited literature suggesting that AURKC mutations may play a broader role in male infertility and highlights the importance of comprehensive genetic evaluation and detailed clinical phenotyping before assisted reproductive therapies.

Conclusion

This case identifies a novel heterozygous AURKC exon 7 mutation in a patient with acephalic spermatozoa syndrome, suggesting a possible new role for AURKC in head–tail coupling. It expands current understanding of AURKC-related infertility and supports the use of comprehensive genetic testing in severe teratozoospermia. Early genetic diagnosis in such patients can inform counseling and management, including consideration of advanced reproductive techniques like ICSI using any residual normal sperm or donor sperm options if necessary.

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Authors' contribution

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Funding acquisition: Amir Reza Vahid Dastjerdi, Nima Vosoughi.
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Writing–review & editing: Saman Abdollahpour, Mehnoosh Shojaei, Sanaz Amiri Marbinis.

Ethics approval

This case report was conducted in accordance with the World Medical Association's Declaration of Helsinki. The patient provided written informed consent for publication as a case report. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that there is no conflict of interest.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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